REMARKS

Claims 1, 3-7, 9 and 12 are pending. New claims 13 and 14 are added. No new matter has been added.

Claims 13 and 14 depend from claim 6 and recite that the "gene" (changed to "nucleic acid" by this amendment) encodes an HCN channel (Claim 13), which in certain embodiments is HCN2 (Claim 14). Support for these claims is found in the specification at paragraph [0035] (see below).

35 U.S.C. Section 112, second paragraph

The Examiner objected to the lack of clarity of claims 6, 7, 9 and 12 arguing that "it is unclear what is encompassed within the term gene." Various passages from the application describe adding a gene encoding a protein or peptide (specifically mentioned are Connexins and HCN) to hMSCs or HeLa cells, which encoded protein or peptide is expressed by the transfected cells:

> [0025] The method may further comprise a step of adding a gene to the mesenchymal stem cells by electroporation. The gene may encode for a connexin, such as connexin 40, connexin 43, and/or connexin 45. . . . .
> [0030] To further define the nature of the coupling hMSCs were co-cultured with human HeLa cells stably transfected with Cx43, Cx40, and $Cx45_7$ and it was found that hMSCs were able to couple to all these transfectants. . . . . .
>
> [0015] FIG. 3. Macroscopic properties of junctions in cell pairs between an hMSC and HeLa cell expressing only Cx40, Cx43 or Cx45. In all cases hMSC to Hela cell coupling was tested 6 to 12 after hours initiating co-culture.
>
> [0035] Alternatively, the hMSCs can be transfected to express genes that produce small therapeutic molecules capable of permeating gap junctions and influencing recipient cells. Further, for short term therapy, the small molecules can be directly loaded into hMSCs for delivery to recipient cells. The success of such an approach is dependent on gap junction channels as the final conduit for delivery of the therapeutic agent to the recipient cells. The feasibility of one such approach was demonstrated by transfecting hMSCs with mHCN2, a gene encoding the cardiac pacemaker channel, and delivering them to the canine heart where they generate a spontaneous rhythm.

It is undisputable that a gene is a nucleic acid and that the gene encodes a protein or peptide (such as connexin and HCN, or "any small therapeutic molecules capable of permeating gap junctions and influencing recipient cells." In order to "influence the recipient cells, the encoded

protein/peptide must be biologically active. Applicants have amended the claims to delete "gene" and recite "a nucleic acid encoding a protein or peptide or biologically active fragment thereof." No new matter has been added.

Applicants point out that tie language "a nucleic acid encoding" was used in the allowed and issued claims Dr. Rosen's US patent **7,122,307 (entitled** *High throughput biological heart rate monitor that is molecularly determined)* to describe "contacting a cardiac myocyte *in vitro* with an amount of a composition comprising a nucleic acid which encodes a HCN channel and MiRP1. . . " See Claim 1.

Applicants respectfully submit that claims as amended overcome the Examiner's rejection and request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102(e) over Taheri et al.

Claims 1, 3-7 and 9 were rejected as anticipated by Taheri et al., U.S. Patent 6690970 (Taheri).

Applicants disagree that Taheri anticipates the cited claims. Applicants refer to the significant differences between the cited claims and Taheri that were pointed out in our response of 2/24/2010. Applicants respectfully submit that the Examiner incorrectly characterizes Taheri by saying that it describes "growing mesenchymal cells in culture and then attaching one end of the strip onto the atrium." This implies that the strip is formed first *in vitro* and then attached to the atrium. This is definitely not what happens in Taheri, nor does this reference even suggest the concept of forming a functional strip of conductive cells *in vitro* that could be then attached to the heart *in vivo*. In order to make this point even more clear, Applicants have amended Claim 1 to further emphasize that the stem cells are grown into a strip *in vitro*, and the strip is then attached to the heart *in vivo*.

"growing mesenchymal stem cells *in vitro* into a strip with two ends"

It is important to note that Taheri is focused on bypassing a specific, limited area in which a conduction block has been identified. FIG. 5 in Taheri "is a diagrammatic view showing a newly formed conductive cell bridge across an area of blockage in an AV node;" This is emphasized in Column 5, next to last paragraph:

> After determination of the location of the ***block site*** 30 in FIG. 2, a plurality of the implantation cells 40 are implanted (seeded). Implantation may be performed by injection using the needle 34, but is preferably performed using the catheter described in more detail below. This same catheter is also preferably used for block site mapping, and may likewise be adapted for cell removal. As shown in FIG. 5, the implantation cells 26 grow to form a conductive cell bridge 50. One end of the cell bridge 50 connects to healthy tissue on one side of the block site 30 while the other end of the cell bridge connects to healthy tissue on the other side of the block site 30. The cell bridge 50 allows electric potential to pass through the block site 30 and reach the ventricular muscles.

As expressly stated above, Taheri injects individual "cells," that then develop functional connections to one another in situ in the heart. Taheri is based on delivering a cells in suspension in a solution) (column 5, line 55, column 6 line 58, column 7 line 7, column 8 line 4, column 8, line 21), not a strip or syncytium of cells or cells on a biomaterial such as a microthread.

In complete contrast to Taheri, Brink et al. first make a functional, conducting strip of cells *in vitro*, which strip is then implanted in the heart thereby forming the atrioventricular bypass tract of the present invention. Figure 2 of Brink et al. shows that the human MSCs form gap junctions with one another in culture even before implantation, and that gap junction currents (Ij) passed between the connected cells.

> *[0014]FIG. 2. Macroscopic and single channel properties of gap junctions between hMSC pairs. Gap junction currents (Ij) elicited from hMSCs using symmetrical bipolar pulse protocol showed two types of voltage dependent current deactivation: (A)-symmetrical, (B): asymmetrical.*

See also Paragraph [0034]. It is an important advancement over the prior art that the present bypass tract can be tested for the ability to conduct current before implantation. By contrast, the individual hMSCs suspended in a solution and injected into or near the site of a block need to still need grow *in situ* to form gap junctions, and there is no guarantee that this will happen every time. With the present invention one does not even need to determine the location of the block with any specificity. It is enough to know that there is a block somewhere between the SA node and AV node that can then be bypassed with the implanted strip of the present invention. This in itself represents another improvement over Taheri and the other prior art.

A further advantage of the present invention is that implanting a functional syncytium (the strip) into the heart will return conductivity to the heart within a significantly shorter time than is

needed for the injected cells of Taheri to "grow" *in situ*, connect and form a conductive bridge, with the inherent risk in Taheri that the syncytium of cells may not even function as intended because there is no way to test for this beforehand.

In the Rule 132 Declaration of Ira Cohen and Michael Rosen, we submit evidence that there is a 6-fold increase in efficiency of cell delivery when cells are grown *in vitro* into a strip such as on a nonreactive biomatrix, before implantation, compared to individual cells that are injected in a fluid medium.

Rejections under 35 U.S.C. § 102(e) over Rosen et al.

The Examiner rejected the cited claims under 35 U.S.C. § 102(e) over Rosen, US2004/0137621. Applicants submit herewith the Declaration of Michael R. Rosen, Richard B. Robinson and Ira S. Cohen and Peter Brink stating that any invention disclosed but not claimed in this reference was derived from the inventor of this application and is thus not the invention "by another."

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected Claims 1, 3-7, 9 and 12 as obvious under 35 U.S.C. § 103 based on *Taheri et al.* in view of Donahue *et al.* (US 2002/0155101). For the reasons set forth above, Applicants submit that Taheri does not teach or suggest key limitations of the present invention and these deficiencies are not compensated for by Donahue. Applicants therefore request that the Examiner withdraw this rejection.

Claims 1, 3-7, 9 and 12 were rejected as obvious under 35 U.S.C. § 103 based on the combination of Rosen and Donahue. However, as the Declaration states, any invention disclosed but not claimed in Rosen was derived from several inventors of this application.

Applicants respectfully submit that the present application, as amended, overcomes the objections and rejections of record and is in condition for allowance. Favorable consideration is respectfully requested. If any unresolved issues remain, it is respectfully requested that the Examiner telephone the undersigned attorney at (703) 622-6528 so that such issues may be resolved as expeditiously as possible. An interview with the Examiner and her supervisory is requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 504213 and please credit any excess fees to such deposit account.

Respectfully Submitted,

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